REMARKS

Reconsideration of the above-identified application, in view of the following remarks, is respectfully requested.

I Status Of The Claims

Claims 100-108, 110-118 and 120-128 have been canceled without prejudice. Claims 99, 109 and 119 have been amended to recite that the claimed methods consist essentially of administering an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof, and pregabalin. New claims 129-134 have been added. Support for the new claims may be found throughout the specification, such as, for example, at paragraph [0039]. No new matter has been added. Claims 99, 109, 119 and 129-134 are pending in this application and are at issue.

II Rejection Under 35 U.S.C. § 103

Claims 99, 101, 109, 111, 119 and 121 stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,441,038 ("Loder") in view of U.S. Patent No. 6,500,853 ("Seehra"). In particular, the Examiner contends that it would have been *prima facie* obvious, in view of Loder and Seehra, to combine milnacipran with pregabalin to treat pain, fibromyalgia syndrome (FMS), and chronic fatigue syndrome (CFS).

The amendments to the claims are believed to place the claims into condition for allowance. In particular, claims 99, 109 and 119 have been amended to recite methods that *consist essentially of* administering pregabalin and an effective amount of milnacipran, or a pharmaceutically acceptable salt thereof. As such, the claims can no longer be construed as encompassing neurotransmitter precursors such as phenylalanine, tyrosine, and tryptophan. Claims 101, 111 and 121 have been canceled, thereby rendering the rejection of these claims moot.

As is acknowledged by the Examiner, Loder teaches that milnacipran is to be "accompanied by either L-phenylalanine or tyrosine." (*See* Office Action at page 4) (Emphasis added). In fact, Loder teaches at numerous points throughout the disclosure that the invention disclosed therein is

directed to a combination therapy that includes neurotransmitter precursors. *See*, e.g., col. 1, lines 42-47, and col. 3, line 21-28. In fact, Loder states, at col. 6, lines 36-40, that:

> [the] effects of *noradrenergic compounds alone* are important but *relatively modest*. Our concept of *combining a noradrenergic drug* like lofepramine or desipramine, *together with a noradrenaline precursor* such as or tyrosine *is much more effective*

(Emphasis added).

As such, one of ordinary skill in the art reading Loder would not have thought to remove the neurotransmitter precursor component from Loder's combination therapy --- certainly, not with any expectation of success.

In this regard, Loder stresses the importance of noradrenaline precursors (such as L-phenylalanine or tyrosine) in Loder's treatment. At col. 5, lines 40-65, for example, Loder chronicles the case history of a patient with CFS, FMS and IBS who was not effectively treated with various drugs, including "serotonin reuptake inhibiting and noradrenaline inhibiting antidepressants," and teaches that the patient only experienced symptom improvement after being co-administered lofepramine *in combination with* L-phenylalanine.

Indeed, all the examples provided by Loder describe the use of a noradrenaline drug in combination with a neurotransmitter precursor (e.g., phenylalanine or tyrosine). It is only through use of this combination therapy (reuptake inhibitor plus the precursor) that the method of Loder is successful.

Overall, and throughout the reference, Loder teaches that that neurotransmitter precursors must be administered in combination with NE reuptake inhibitors and dual serotonin norepinephrine reuptake inhibitors, in order to achieve effective treatment.

Accordingly, because pending claims 99, 109 and 119 have been amended to specify that the recited methods exclude additional active agents (such as L-phenylalanine and tyrosine) other than

(1) pregabalin and (2) milnacipran, or a pharmaceutically acceptable salt thereof, the pending claims are believed to be patentable over the cited references.

The Seehra reference fails to cure the deficiencies of Loder. In particular, Seehra is directed to the use of substituted indole and indoline derivatives for the treatment of inflammatory conditions. (*See*, for example, the Abstract of Seehra). Seehra discloses that pain may be treated by administering "a *compound of this invention* alone or in combination with one or more additional pharmaceutically effective agents" (col. 102, lines 37-41, emphasis added). The "compound of this invention" is the substituted indole/indoline derivative. Examples of additional effective agents that may be combined with the indole/indoline derivative include analgesics, anti-angiogenic agents, anti-neoplastic agents and anti-epileptic agents (col. 102, lines 37-46), one of which happens to be pregablin. Thus, the disclosure of Seehra would teach one skilled in the art that the substituted indole/indoline derivative is the primary active agent and is necessary for effective treatment of a disorder such as pain. At best, Seehra teaches the administration of pregabalin *in combination with* a substituted indole/indoline derivative.

Moreover, contrary to the concerns of the Examiner, Applicants have not simply combined two compounds that are used for the same purpose to form a combination used for the very same purpose. Milnacipran and pregabalin are two drugs that have different mechanisms of action and fall within distinct drug classifications. Milnacipran is a serotonin-norepinephrine reuptake inhibitor that has been used for the treatment of *depression*. In contrast, pregabalin, which acts via binding to calcium channels, has previously been used to treat *seizures*. Thus, at the time of the present invention, one of ordinary skill in the art would have had no expectation that milnacipran and pregabalin could be combined to effectively treat fibromyalgia syndrome. Moreover, there is no suggestion in the art to provide this specific combination. Thus, the treatment of fibromyalgia by administering only milnacipran in combination with pregabalin would not be obvious to one skilled in the art.

Accordingly, the cited references, when taken alone or together, fail to teach or suggest the treatment of FMS, CFS, or pain using a method that consists essentially of administering pregabalin and milnacipran, or a pharmaceutically acceptable salt thereof.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

III Conclusion

Therefore, all objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Should any issues remain unresolved, the Examiner is encouraged to contact the undersigned attorney for Applicants at the telephone number indicated below in order to expeditiously resolve any remaining issues.

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Respectfully submitted,

By _____

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